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Role of Metformin in Polycystic Ovary Syndrome

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Abstract

Introduction and purpose:

PCOS is identified by the presence of underdeveloped follicles in the ovaries caused by a lack of ovulation, and it is linked to heightened production of androgens in the ovaries. The observable symptoms of PCOS encompass irregular or absent menstrual cycles, obesity, and indications of excess androgens such as acne or oily skin. Metformin could be advantageous for a specific group of women with PCOS.

The aim of this study is to summarize the current knowledge regarding the effectiveness of metformin in the treatment of PCOS based on available scientific literature.

A brief description of the state of knowledge:

Metformin indirectly aids in enhancing ovulation and alleviating long-term metabolic issues, although its impact is considered moderate. Metformin also diminishes the levels of particular markers linked to arterial issues and chronic inflammation beneath the surface. This indicates a potential decrease in the continual risks of type 2 diabetes (DM) and cardiovascular disease (CVD) for women dealing with PCOS.

Summary (conclusions):

Managing PCOS involves personalized targets due to its diverse nature. In clinical practice, metformin is a recommended first step for managing PCOS in overweight or obese patients, particularly when oral contraceptives are not suitable or insulin resistance is evident.

Keywords: Polycystic Ovary Syndrome; Metformin; Insulin Resistance; Ovulation

Metformin

For over 60 years, metformin has been used as a substance to lower blood glucose levels. [1] It is considered a safe and relatively inexpensive drug in relation to its effectiveness. A distinguishing feature (compared to other drugs that lower blood glucose levels) is the lack of a hypoglycemic effect and a beneficial impact on patients' body weight. [2] When comparing metformin to other antidiabetic drugs, it is worth noting that it significantly demonstrates a vascular risk reduction effect in diabetic patients compared to others. [2,4] Furthermore, the use of metformin is not limited to diabetes. It is also used in the treatment of conditions such as obesity, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, and PCOS. [3] Constantly, new, previously unknown applications of metformin are being discovered, such as its protective effect on bones, especially in the early stages of rheumatoid arthritis (RA). [5]

The administration of metformin is associated with gastrointestinal side effects, including nausea, loss of appetite, and diarrhea, affecting approximately 10% of patients and potentially leading to treatment discontinuation. [7] Furthermore, it's worth noting that while metformin is approved as a first-line therapy for Type 2 diabetes mellitus, its use in PCOS is considered off-label. Therefore, obtaining a signed informed consent is crucial when prescribing metformin to women with PCOS. Additionally, in cases where surgery is planned, metformin treatment should be halted 48 hours before the procedure due to the risk of metabolic acidosis.

PCOS

Polycystic ovary syndrome (PCOS) brings about significant complications for women, with approximately one in every 5–6 facing serious challenges related to infertility and irregular menstrual cycles. Contributing factors on a global scale include stress, obesity, and hormonal fluctuations [24]. PCOS, categorized as an endocrine disorder, affects women between the ages of 18 and 44 [25], impacting 5–15% of females worldwide [26]. Hormones play a crucial role in maintaining ovarian function and regulating the menstrual cycle, essential for fertility. Disturbances in female hormonal levels can disrupt ovarian function, leading to cyst formation within the ovarian sac. Additionally, PCOS can result in an elevation of androgen, a male hormone, beyond its normal range in affected females [27].

The action of metformin at the cellular level in PCOS

Currently, it is known that insulin resistance is highly prevalent among patients with PCOS. Due to this fact, one of the groups of drugs used in this disorder includes preparations that

improve insulin sensitivity, particularly applied in obese patients with PCOS accompanied by insulin resistance. It has been confirmed that in these patients, metformin has a positive impact on ovulation, normalization of the menstrual cycle, and a reduction in serum androgen levels [6]. Metformin's positive impact stems from its ability to mitigate the overstimulation of insulin on the ovaries and directly influence ovarian function. Studies have shown that insulin directly triggers various steroidogenic enzymes in the ovary, including CYP17, 3 β -HSD, and the StAR protein. By enhancing insulin sensitivity, metformin effectively diminishes the activity of CYP17. [8] Additionally, metformin hinders the synthesis of androstenedione by directly affecting ovarian theca cells. It also diminishes the FSH-induced activity of 3 β -HSD, StAR, CYP11A1, and aromatase in both rat granulosa cells and women with PCOS. This leads to a reduction in basal and FSH-stimulated progesterone levels, subsequently impacting estradiol levels. [8]. The molecular pathways through which metformin directly acts on the ovary remain elusive. Recently, it has been demonstrated that metformin treatment increases AMPK activity in rat granulosa cells, leading to subsequent reduction in steroid synthesis [10,11]. However, it is still unclear whether this effect is AMPK-dependent or not. When evaluating the drug's impact on PCOS, pharmacogenetic aspects of metformin action should be considered. Indeed, data from the Pregnancy in PCOS (PP-COS) study have shown that a polymorphism in the LKB1 gene is associated with a significant reduction in the likelihood of ovulation in PCOS patients treated with metformin [12].

Interestingly, it has been demonstrated that metformin reduces the risk of miscarriage in women with PCOS who are in high-risk pregnancy by increasing certain factors essential for implantation and maintaining pregnancy, such as levels of IGFBP-1 and glycodelin, as well as blood flow in the uterine artery [8,9]. On the other hand, metformin decreases risk-increasing factors for miscarriage, such as the expression of androgen receptors in the endometrium, levels of plasminogen activator inhibitor-1 (PAI-1), and plasma endothelin-I (ET-1). In most of these effects, the improvement in insulin sensitivity induced by metformin likely plays an intermediary role.

Treatment methods in PCOS

The choice of drugs or procedures for treating PCOS is primarily determined by the patient's symptoms or the specific clinical goals, whether it involves addressing infertility, regulating menstrual irregularities, alleviating symptoms related to hyperandrogenism, or pursuing

treatment for obesity.

For women aiming to get pregnant, clomifene continues to be the initial treatment of choice. It functions as an estrogen receptor modulator, directly influencing the hypothalamic-pituitary axis, acting swiftly and efficiently. About 75% of pregnancies in individuals using clomifene occur within the first three months of treatment. [28] Another medication employed for PCOS patients seeking to regain fertility is metformin, and its efficacy becomes noticeable after a treatment duration of six months. [28, 29] While earlier reports did not validate the impact of metformin on clinical symptoms associated with hyperandrogenism, more recent data suggest such effects, particularly in mitigating skin issues like hirsutism, acne, and acanthosis nigricans. [28] Additional treatment alternatives for women infertility due to PCOS include the use of gonadotropins to stimulate ovulation or laparoscopic surgery for those who do not respond well to pharmacological approaches. Laparoscopic methods capable of effectively inducing ovulation encompass procedures such as ovarian biopsy and electrocautery, laparoscopic ovarian drilling, transvaginal hydrolaparoscopy, ultrasound-guided transvaginal ovarian needle drilling, or laparoscopic ovarian multi-needle intervention. [28] [30]

Individuals with PCOS who aren't aiming for pregnancy are often recommended oral contraceptives (OCP) to effectively regulate menstrual cycles, diminish hyperandrogenism, and lower the risk of endometrial hyperplasia. [28] The visible effects of excessive androgen production, such as hirsutism, acne, alopecia, and acanthosis nigricans, are common reasons why PCOS patients seek medical assistance. These manifestations also significantly contribute to a decrease in their overall quality of life, leading to chronic stress and mental health issues, including depression. [31] The pharmacological approaches to address these problems typically involve the use of antiandrogen medications like cyproterone acetate in combination with ethinyl estradiol (OCP), spironolactone, or metformin. [32]

Metformin, hyperinsulinemia and IR

Insulin resistance (IR) and secondary hyperinsulinemia impact about 65-70% of women with PCOS [3], and a substantial portion of these individuals also contend with obesity, exacerbating their insulin resistance. Insulin stimulates the production and release of androgens in ovarian theca cells, concurrently suppressing the hepatic production of sex hormone-binding globulin. The heightened levels of intraovarian androgens disrupt the normal process of folliculogenesis. [4] Additionally, hyperinsulinemia may directly

contribute to premature follicular atresia and the arrest of antral follicles.[5] Consequently, anovulation occurs, leading to unopposed estrogen production and increased endometrial proliferation in women with PCOS, thereby raising the risk of endometrial hyperplasia.

In line with the elevated rates of insulin resistance and obesity in PCOS patients, there is a heightened prevalence of conditions such as impaired glucose tolerance (IGT), type 2 diabetes [13, 14, 15], dyslipidemia, and chronic subclinical inflammation. [21,22] Recognizing a dysmetabolic pattern characterized by elevated triglycerides, slight alterations in low-density lipoprotein (LDL), and reduced high-density lipoprotein (HDL) [22] is crucial for providing guidance on lifestyle modifications to patients. This awareness also proves valuable in long-term patient monitoring, establishing a baseline for comparison. Additionally, a significant subset of individuals with PCOS exhibits features consistent with metabolic (or dysmetabolic) syndrome. [23]

The positive impact of metformin on insulin sensitivity has been observed in non-diabetic women with polycystic ovary syndrome (PCOS). Utilizing metformin is associated with improved menstrual regularity, enhanced ovulation, and a decrease in circulating androgen levels. [17,19] These metabolic advantages are particularly notable in conjunction with weight loss, and notably, metformin itself may contribute to an increased effectiveness of weight loss. [18,20]

The application of metformin in women grappling with PCOS typically amplifies insulin sensitivity and leads to reductions in both weight and BMI. [20] In a comprehensive meta-analysis involving 13 studies, metformin exhibited positive effects on fasting insulin levels, blood pressure, and LDL cholesterol, [33] potentially influenced by alterations in body weight. A meta-analysis by Salpeter et al. [34] encompassing 31 trials with 4570 participants over 8267 patient-years aimed to evaluate metformin's impact on metabolic risk. Although no significant differences surfaced between PCOS and non-PCOS individuals, it's crucial to note that none of the trials specifically delved into metformin's influence on the incidence of type 2 diabetes. The meta-analysis disclosed that women with PCOS witnessed a 5.3% reduction in BMI, a 2.6% average dip in fasting glucose, and a substantial 19.7% improvement in insulin resistance gauged by the HOMA (HOMA-IR) index. Despite a non-significant 5.7% decrease in fasting insulin, the results were noteworthy. Furthermore, HDL cholesterol saw an average uptick of 9.4%, while triglycerides experienced an 11.9% decrease. These trends were generally comparable between PCOS and non-PCOS individuals, except for fasting insulin, which demonstrated a more pronounced improvement (16.1%) in non-PCOS cases.

Metformin and weight loss

Metformin is suggested to contribute to weight loss in PCOS patients. In a study by Tan et al. [20], data from three groups of PCOS patients—lean, overweight, and obese—showed a notable link between metformin use and a decrease in body weight and BMI among those in the overweight and obese categories. Another study indicated that metformin had the capacity to reduce body weight, extending its efficacy to nonobese women with PCOS. [35]

Metformin and subfertility

Metformin likely aids in improving ovulation induction for women with PCOS through several actions. This includes reducing insulin levels and altering insulin's influence on processes such as ovarian androgen biosynthesis, the proliferation of theca cells, and endometrial growth. Additionally, it may have a direct effect by inhibiting ovarian gluconeogenesis, thereby reducing ovarian androgen production. [40]

In an in-depth examination, metformin alone has shown a significant benefit in stimulating ovulation in women with PCOS. However, the existing evidence is limited in determining its influence on enhancing pregnancy rates. [41]

Metformin and the risk of cardiovascular events

Considering the heightened risk of cardiovascular disease (CVD) associated with metabolic syndrome and insulin resistance (IR), it becomes crucial to factor in IR and long-term health considerations when choosing medical treatments for overweight women with PCOS. [36] At the outset, many PCOS patients exhibit some form of dyslipidemia, often characterized by diminished levels of HDL cholesterol and slightly elevated levels of LDL cholesterol, triglycerides, and total cholesterol. [37] Metformin has been proven to enhance endothelial function, as evaluated through brachial arterial flow-mediated vasodilation. [38] Additionally, there are documented improvements in coronary microvascular function and coronary flow rate associated with the use of metformin. [39]

Metformin and endometrium

Excess insulin levels have been found to stimulate the growth of the endometrium, potentially leading to increased proliferation. The use of metformin is theorized to impact the endometrium, with a potential dual effect of improving the chances of successful pregnancy implantation and lowering the long-term risks associated with uncontrolled endometrial

proliferation. [42] In a study led by Palomba et al. [43], 37 individuals with anovulatory PCOS underwent a six-month treatment with metformin. Their outcomes were compared to those of 30 control subjects matched for age. The investigation delved into uterine vascularization, endometrial thickness, and endometrial pattern. The results highlighted that metformin led to enhancements in multiple facets of endometrial receptivity among PCOS patients. Notably, there was no substantial effect observed on endometrial thickness.

Metformin and other symptoms of hyperandrogenism

There is substantial evidence affirming the positive impact of metformin on the hyperandrogenism observed in individuals with PCOS.

In a research comparison involving nonobese, non-insulin-resistant women with PCOS, individuals receiving metformin alone (2250 mg/day), rosiglitazone alone (4 mg/day), and a combination of both drugs exhibited significantly lower mean serum-free testosterone levels compared to those in the placebo group. [44]

Conclusion

Addressing polycystic ovary syndrome, a prevalent condition impacting a significant number of women globally, continues to revolve around specific targets that can differ from one person to another. The ideal scenario involves addressing the root cause, but the current limited understanding of the syndrome's pathogenesis poses a hurdle to achieving this comprehensive approach.

Metformin indirectly helps with better ovulation and reducing long-term metabolic issues, though its impact is moderate. Managing metabolic syndrome in women with PCOS involves closely controlling blood pressure, losing weight, adjusting diet, and, if needed, using medications for lipid modification. Metformin also lowers the levels of certain markers related to artery problems and underlying chronic inflammation. This suggests it might lower the ongoing risks of type 2 diabetes (DM) and heart disease (CVD) in women with PCOS, but we're still waiting for comprehensive, long-term studies to confirm these effects. From a clinical perspective, the administration of metformin should be considered as an initial intervention in PCOS patients (overweight or obese), especially when oral contraceptives are contraindicated or insulin resistance is present.

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